International Forum

Vox Sang. *39:* 229–240 (1980)

Which are the Parameters to be Controlled in Red Cell Products (Whole Blood, Red Cell Concentrates, Washed Red Cells, Leucocyte Poor Red Cell Concentrates, Frozen Red Cells) in Order that They May be Offered to the Medical Profession as Standardised Products with Specified Properties?

It has become an established practice to consider plasma derivatives as biologicals of human origin and to subject them to strict quality controls. There is an increasing – and justified – tendency to apply the same principles to cellular blood components. Which are the parameters to be controlled in red cell products (whole blood, red cell concentrates, washed red cells, leukocyte-poor red cell concentrates, frozen red cells) in order that they may be offered to the medical profession as standardised products with specified properties?

William L. Bayer. The present technical standards of the American Association of Blood Banks [1] and United States Bureau of Biologics [2] are in my opinion sufficient to meet the needs of the medical practice for red cell preparations adequate for the clinical purposes for which they are transfused.

References

1 Standards for Blood Banks and Transfusion Services; 9th ed. (AABB, Washington 1978).
2 Code of Federal Regulations 21, Food and Drug (US Government Printing Office, Washington 1978).

William L. Bayer, MD
Director
Community Blood Center of Greater Kansas City
4040 Main Street
Kansas City, MS 64111 (USA)

B. Genetet and P. Mannoni. French law imposes only a few requirements to which whole blood or concentrated red cell suspensions used for transfusion must conform. Apart from the need to screen blood for syphilis and hepatitis B virus and to ensure immunologic donor-recipient compatibility, the only restriction imposed by law is that a minimum of 70% injected cells be present in the recipient's circlation 24 h post-transfusion, a criterion of *in vivo* survival which takes little account of red cell oxygen carrying capacity. This relative freedom from legal impositions is, however, being somewhat eroded: a bill was passed on February 20, 1980 [3] requiring blood banks to set up accurate protocols for the preparation of unstable components and for quality control procedures to be performed at each stage of their preparation. Quality control has thus become part of blood banking in France. To be effective it should assess three main factors: (1) functional adequacy: this is an area hitherto neglected to a certain extent and concerns oxygen transport and release and microcirculation properties, namely red cell deformability; (2) quantitative adequacy; this concerns the quantities of each blood product per unit of whole blood or packed red cells, and (3) transfusion hazards: this covers a number of areas, including im-

munology, bacteriology, virology and possibly toxicology.

Tests are therefore needed to determine transfusion efficacy and ascertain the absence or virtual absence of risk.

Briefly, blood quality is determined by: choice of donor; blood collection [6], transfer and storage conditions; and technical stringency in the preparation of washed or frozen concentrated red cell suspensions, and leukocyte-poor and platelet-poor red cell suspensions. Much could be said about quality control in each of these five areas. Suffice it here simply to stress the need for such controls.

It goes without saying that not all units need be submitted to control, but strict adherence to standard sampling techniques is, of course, a key element in good quality control.

Functional Tests

Estimations of intracellular red cell pyruvate kinase activity and glucose concentration are necessary for an overall assessment of the erythrocyte metabolic potential on which the red cell's functional properties depend. Red cell oxygen delivery capacity must also be evaluated. *Valtis and Kennedy* [8] have shown that the oxygen unloading capacity of red cells is a function of the duration of blood storage at 4 °C. Other studies [1] have shown clearly that the oxygen delivery capacity of red cells also depends on the anticoagulant-preservative solution used. Research on erythrocyte metabolism [7] has furthermore pointed to 2,3-diphosphoglycerate (DPG) concentration as a key factor and one that should be measured as part of the control procedure. It is also necessary to measure red cell pH and P_{50} and to check the efficiency of the NAD/NADH system which determines the integrity of the methemoglobin-reductase system and consequently of hemoglobin function.

Red cell flow characteristics can be assessed by chemical and by physical methods. As the mainstay of red cell deformability ATP must be measured in any control procedure. Some investigators also recommend measurement of the red cell nucleotide concentration [5]. K^+ and Na^+ should also be determined, as they reflect the efficiency of the different enzyme pathways involved, notably the sodium pumps.

Most of the physical tests are simple to perform. One such test is light microscopic examination of red cell shape and determination of the proportion of echinocytes. For complete quality control, scanning electron microscopic examination can give valuable information, including the spherocyte count. Measurements of red cell osmotic resistance, filterability [2] and viscosity complete the checklist for control of flow properties. In addition, determination of the filtration pressure is useful in assessing the volume and number of aggregates in the unit, although this test is not universally believed to reflect the properties of transfused blood *in vivo* [4].

Quantitative Tests

The second set of tests required for good quality control concerns the quantity of hemoglobin transfused. Once conditions for good red cell oxygen-releasing capacity and flow characteristics are met, the effectiveness of transfusion will depend on the number of hemoglobin molecules injected. This number can be calculed from the red cell count and the measurement of hemoglobin content, from the weight of the blood unit and from the respective volumes of blood components (residual plasma and erythrocytes).

Transfusion Hazards

The third set of tests concerns transfusion risks, first and foremost the immunologic risk, although with routine crossmatching this hazard has been greatly reduced. ABO grouping and Rh or Kell typing and the search for irregular antibodies in whole blood have become standard transfusion screening practice. The risks of bacterial, viral or parasitic contamination are much greater and therefore make far more imperative demands on quality control. Culturing in suitable media provides adequate bacteriologic screening, although the risk of bacterial contamination has been greatly reduced with the advent of sealed plastic transfer systems. Testing for HBeAg and HBc antibody should be mandatory, as is testing for HBsAg, since post-transfusion viral hepatitis is currently a major transfusion hazard. Screening for plasmodia by immunofluorescence techniques is advisable. Other

less vital quality control tests include measurement of plasma ammonium and hemoglobin.

In preparing specific red cell units, as mentioned above, certain tests should be added to the above list (although the short interval between preparation and injection of washed erythrocytes makes bacteriologic testing difficult), namely, determination of WBC and residual platelet counts (for leukocyte-poor, platelet-poor and washed packed cell preparations) and of glycerol content in frozen red cells.

Conclusions

Current blood banking in France includes compulsory immunologic and viral screening tests, in addition to the control procedures recommended above. All these tests, however, cannot be performed on every blood unit to be transfused. A sampling procedure is necessary to determine which and how many units have to be tested. However, each and every unit should be checked at least for weight, relative volumes of components, and Hb concentration and content.

References

1 Genetet, B. et Mannoni, P.: La transfusion, pp. 94–104 (Flammarion, Paris 1978).
2 Gueguen, M; Genetet, B.; Le Garzic, J. et Marcel, G. A.: Filtrabilité du sang conservé. Nouv. Presse méd. *7:* 2256–2257 (1978).
3 Journ. Off. Rep. fr., 15 mars, p. 2626 (1980).
4 Risberg, B.: Screen filtration pressure and quantity of micro aggregates: a nonexisting relationship. Transfusion *19:* 749–753 (1979).
5 Saint-Blancard, J.; Allary, M.; Bouchet, J. et Fabre, G.: Les nucléotides adényliques comme indicateurs de la qualité des sangs ACD et CPD conservés. Rev. fr. Transf. *XVII:* 137–145 (1974).
6 Standards for Blood Banks and Transfusion Services (AABB, Washington 1978).
7 Valeri, C. R.: Viability and function of preserved red cells. New Engl. J. Med. *284:* 81 (1971).
8 Valtis, D. C., and Kennedy, A. C.: Defective gas transport function of stored red blood cells. Lancet *i:* 119 (1954).

Dr. B. Genetet, Directeur
Centre régional de transfusion sanguine,
rue Pierre-Jean-Gineste
F–35000 Rennes (France)

H. H. Gunson. The source material for red cell products is the donation of whole blood. Consideration of quality control procedures, therefore, must begin with the donor. Detailed medical examination of donors is not always practical before blood donation and one is often dependent upon the donor for history of past or current illness which may exert undesirable effects on the recipient of the blood. Various tests can be applied to the donation, e.g., syphilis, hepatitis Bs antigen, and in many countries these are routine. The sensitivity of the tests, e.g., for HBsAg may vary, however, and uniformity of testing using the most sensitive test available would be an advantage. Other tests applied to the blood donation may vary from centre to centre, e.g., cytomegalus antibody tests, provision of O Rh-negative blood which is Kell-negative and contains a low titre of anti-A and anti-B. The provision of blood characterised by such tests often depends on local transfusion practice – standardisation can only be achieved by wide acceptance of the procedure as significantly beneficial to the patient.

One test widely practised prior to donation is the estimation of haemoglobin concentration of the donor. In Great Britain and certain other countries, male donors are rejected if the haemoglobin concentration is below 13.5 g/dl, and femal donors if the concentration is below 12.5 g/dl. Thus, a variable haemoglobin concentration and packed cell volume will inevitably occur in the whole blood donations. Furthermore, the common practice of removing a given volume of plasma from whole blood donations to prepare red cell concentrates perpetuates the variability in that product. Thus, in the British Pharmacopoeia, concentrated red cells are defined as the preparation resulting from removal of not less than 40% of the plasma (and anticoagulant) from a unit of whole blood. This definition can embrace a wide range of red cell concentrates and perhaps, with advantage, this product should be defined in terms of the packed cell volume of the preparation.

Whole blood contains many cellular elements and plasma factors other than red cells and each

may be subject to biological variation. Other factors which may introduce variables include the care taken and ease of venepuncture, the length of time for the donation and the period elapsing before the donation is cooled to 4 °C. Such factors, however, probably affect the viability of red cells less than other more labile constituents; thus, a period of 6 h at ambient temperature prior to refrigeration of blood at 4 °C had little adverse effect on post-transfusion survival of red cells [1]. However, it must be remembered that there are differences between donors in the post-transfusion red cell survival [2]; a factor which cannot be subjected to standardisation.

Various anticoagulant/preservative solutions are used for red cell preparations, commonly acid citrate dextrose (ACD) or citrate phosphate dextrose (CPD) with or without the addition of adenine. The proportion of blood to anticogulant is an important factor affecting survival of the red cells and careful monitoring of the filling of containers is essential. Biochemical changes occur as a result of red cell storage *in vitro* and the rate change varies with the anticoagulant used. Thus 2,3-DPG levels fall more rapidly in blood stored in ACD compared with that in CPD: ATP levels also fall but are maintained at a higher concentration when adenine is added. Whilst ATP is one factor which plays a part in red cell viability, 2,3-DPG and ATP influence the oxygen-transport function of the red cell. The significance of maintaining adequate levels of 2,3-DPG in transfusion practice has been the subject of considerable debate and it may have importance in transfusions in certain clinical situations [3]. It has been suggested that the use of preserved red cells with elevated levels of 2,3-DPG and ATP, prepared by incubating with solutions containing adenine, pyruvate, inosine, glucose and phosphatees followed by saline washing are functionally superior to blood stored under normal conditions [4].

Additional treatment of processing of red cell preparations such as that cited above or following the reconstitution of frozen cells requires adequate quality control. When several solutions come into contact with the red cells in association with cryopreservation or other treatment, documentation of all reagents should be meticulously carried out. The acceptability of the processed red cells for transfusion should be evaluated and various tests have been recommended for frozen-thawed red cells [5] which depend on the use of osmolality determinations of the final supernatant compared to normal serum or the degree of free haemoglobin, with a definition of acceptable limits.

All procedures involving 'open' systems will lead to the increased risk of bacterial contamination. It is not practical to perform cultures on such preparations prior to transfusion and reduction of storage time to 24 h after processing is usual. This applies particularly to frozen-thawed red cells and leucocyte-poor blood. The latter preparation is usually administered to patients suffering febrile reactions due to leucoagglutinins and may be prepared by filtration through scrubbed nylon or cotton wool filters or by saline washing procedures with or without prior sedimentation with rouleaux-inducing agents such as dextran or hydroxyethyl starch. Frozen-thawed red cells are also leukocyte poor. It is not surprising that uniformity of the product is difficult to achieve when it is prepared in so many ways. It must be borne in mind that the purpose of the leucocyte-poor is to transfuse the patient with red cells containing few leucocytes; it was shown by *Dausset et al.* [6] and has been confirmed by others that removal of at least 90% of the leucocytes in a unit of blood may be necessary to prevent febrile reactions due to leucoagglutinins. With the availability of automated cell counters measurement to ensure that this criterion is fulfilled could be carried out prior to transfusion.

In conclusion, there is a biological variation associated with red cell preparation which is difficult, and in some instances impossible, to quality control to effect a standard product. However, with the use of increasingly complex procedures and with products for specific functions, quality control is feasible and it is important that it be carried out both from the point of view of the safety of the transfusion and the predictability of the clinical effect of the transfused product.

References

1 Avoy, D. R., Ellisor, S. S.; Nolan, N. J.; Cox, R. S., Jr.; France, J. A.; Harbury, C. B.; Schrier, S. L., and Pool, J. G.: The effect of delayed refrigeration on red cells, platelet concentrates

and cryoprecipitable AHF. Transfusion *18:* 160–168 (1978).
2 Dern, R. J.; Gwinn, R. P., and Wiorkowski, J. J.: Studies on the preservation of human blood. Variability in erythrocyte storage characteristics among healthy donors. J. Lab. clin. Med. *67:* 955–965 (1966).
3 International Forum: Vox Sang. *34:* 111–127 (1978).
4 Zaroulis, C. G.: The importance of red cell 2,3-diphosphoglycerate in transfusion therapy. Haemotherapy in trauma and surgery, pp. 43–55 (AABB, Washington 1979).
5 Roberts, S. C.: Cryopreserved red blood cells: a blood component. A seminar on blood components, pp. 37–52 (AABB, Washington 1977).
6 Dausset, J.; Fonseca, A. et Brecy, H.: Elimination de certains chocs transfusionnels par l'utilisation de sang appauvri en leukocytes. Vox Sang. *2:* 248–256 (1957).

H. H. Gunson, DSc, MD
Director
Regional Transfusion Centre
Roby Street
Manchester M1 3BP (England)

William V. Miller. Red blood cell transfusions are given for the purpose of increasing oxygen delivery to tissues. Red blood cell concentrates are, in the majority of circumstances, the best product performing this function but special patient needs – such as expansion of the blood volume (or, conversely, the prevention of circulatory overload) or transfusion with unwanted cellular and plasma constituents – often require selection of other transfusion products. In any case, the transfusionist has certain expectations which must be met: (1) the dose size must be consistent in order to provide predictable increments in the erythrocyte mass; (2) erythrocyte survival should be as nearly normal as possible so that the frequency of transfusions can be predicted, and (3) the erythrocytes should function normally so that their expected benefits to tissue oxygenation can be achieved.

Furthermore, the transfusionist expects that it should be possible to minimize adverse effects. It may be necessary to alter the plasma volume of the red cell concentrate to meet the patient's physiologic state; that is, the hypovolemic patient may require that the plasma be retained, or the patient with cardiac or renal disease may require that plasma volume be further reduced.

Finally, it may be necessary to reduce the concentration of other cellular constituents to prevent febrile non-hemolytic transfusion reactions or alloimmunization.

The quality control procedures used to assure consistency of the final product must be sufficiently comprehensive to meet all these needs but not sufficiently complicated so as to unduly complicate or add unnecessarily to the cost of transfusion. The *total volume* of the product should be clearly displayed on the label, accurate to plus or minus 10%. This is, of course, best done by accurately weighing the product at the time of collection and separation. Since the *hematocrit* of the final product is important, not only to the calculation of the dose but to the function and survival of the red cells at the end of the period of storage – especially in CPDA-1 – measurement of the final hematocrit and its retention in a fairly narrow range is desirable for all red cell components as well. Assuming careful donor selection and reasonable attention in the component preparation laboratory, it should not be necessary to measure each dose prepared but only enough units to assure consistency. For those components in which cellular reduction is essential (leukocyte-poor red blood cells, for example), standards of reduction must be agreed upon, and a sufficient number of units measured to assure that the desired cellular reduction has been consistently achieved.

The best indicator of erythrocyte survival is the degree of maintenance of adenosinetriphosphate (ATP) levels and the best available predictor of oxygen delivery function is the maintenance of 2,3-diphosoglycerate (2,3-DPG) levels. Existing anticoagulant preservative solutions are so formulated as to provide acceptable maintenance of these essential nutrients so that it is not necessary to measure them in the processing laboratory. Products prepared so as to assure accurate and consistent final volumes and hematocrits and prepared by published and recommended proccesses should assure maintenance of both ATP and 2,3-DPG.

In summary, the quality control of erythrocytes components should concentrate on measure-

ment of the initial volume, the final volume, and the hematocrit so as to assure consistent dosage size, appropriate red cell survival, and necessary red cell function. The label of the final product must indicate the final volume and hematocrit accurate to at least plus or minus 10%. In those products in which a cellular component or plasma is removed for special transfusion requirements, the label should clearly indicate the technique and degree of such removal. Routine use of sophisticated biochemical measurements and routine measurement of volume and hematocrit on each transfusion product is unproductive and unwarranted.

William V. Miller, MD
Director
American Red Cross
Missouri/Illinois Regional Blood Services
4050 Lindell Boulevard
St. Louis, MO 63108 (USA)

Byron A. Myhre. Blood banks must routinely perform some quality control procedures on all blood components and derivatives to contribute to the safety and therapeutic effectiveness of the final product. However, the amount and type of quality control depends greatly on the product being prepared. Plasma derivatives, i.e., chemical fractions, begin as a pool of plasma made from a number of donoors and represent a large volume (often 1,000 liters or more). Therefore, it is relatively easy to draw off aliquots during the fractionation process and analyze them. Further, after fractionation most of the derviatives are heat treated and filtered, thereby decreasing the possibility of contamination. On the other hand, red blood cell components (and other formed elements as well) cannot be pooled or heat treated and therefore must be treated as individual lots. Performing analyses on these components requires either a noninvasive method or else the sacrifice of the unit. For this reason, most quality control procedures for red cells should be limited in number, and must be carried out by a statistical sampling of individual components rather than a serial sampling of each batch in production.

General

A differentiation should be made between quality assurance procedures which are nice to know, those which are easy to perform, and those that provide patient safety. They are not necessarily similar [1].

Quality assurance procedures should be significant and effective. Meaningless quality assurance is a waste of time and money. Enough units should be studied to assure the effectiveness and safety of the components, and yet not waste a number of units which could be transfused. The number of units tested should be proportional to the number processed and not limited to any arbitrary number.

Much of the safety of red cell components begins with the use of adequate criteria to screen and process donors and the use of donors who will not lie. Usually, this means volunteer donors. The donor should not have a history of hepatitis nor any other disease which could be transmitted through the blood itself.

At the time of donation, the venepuncture site should be prepared in such a way that the maximum number of skin organisms are removed. Under no circumstances should the prepared site be subsequently touched with the finger. Finally, the donor tubing should be tightly sealed and the blood unit promptly refrigerated if it is not to be used as a source of platelets. All of these precautions will prevent the unit from being contaminated.

Previous studies must have been carried out to assure that the anticoagulant is stable and sterile, and that the plastic has been studied so that the bag system has been shown to be capable of preserving a normal unit of blood for its acceptable storage time with minimal hemolysis. These studies have been performed at the time the bag was accepted for use.

Quality assurance procedures need to be tailored to the eventual use of the product. For example, the amount of plasma in a unit of red cell concentrate may be perfectly acceptable to the average patient, yet may cause a serious reaction in a patient with anti-IGA. On the other hand, it would be silly to require all units of red cell concentrates to have very low levels of plasma so that it would be acceptable for this specific patient.

Let us now consider the individual red cell components.

Red Cell Concentrate

This component is used primarily when a patient needs a maximal number of red cells in a

minimal volume. The most important measurements are therefore total volume (weight) and total red cell mass (hematocrit). These should be checked periodically on random units to show that the resulting product is adequate. Occasionally, there is need for units with low levels of electrolytes or other plasma-soluble metabolites. These should be prepared just prior to transfusion and should be assayed at that time. Periodic observations should be made on all red cell concentrates which are stored to show that there is only a small amount of red cell autolysis at that specific hematocrit.

Washed Red Cells

Usually, these cells are washed to remove protein (for use in a patient with anti-IgA) or to remove leukocytes (for a patient with symptomatic leukoagglutinins). As with all red cell units, it is necessary to determine periodically the number of red cells present to make certain that not too many of them have been lost during washing. Further, washing usually requires that the blood unit be entered, so sterility testing must be done if the washed cells are to be stored for more than 3–6 h. We have found that this testing can be done easily with a radioisotopic method [2] which gives a reliable answer quickly. Sterility testing need not be done if the washing solutions are known to be sterile, and if the cells are to be transfused immediately. Protein determinations and/or leukocyte counts should be done periodically to assure that these components have been decreased. There are no universally accepted guidelines as to how much of these components should be removed to prevent clinical reactions. Therefore, it probably is best to remove as much as possible, and keep records for future studies.

Leukocyte-Poor Red Cell Concentrates

Periodic hematocrit determinations and leukocyte counts should be made on these units, but they need not be studied for sterility unless the unit has been entered.

Frozen Red Cells

Most of the studies previously listed should be performed on this component, but in addition, the glycerin content should be determined occasionally. There is a certain amount of controversy as to how much of this constituent is acceptable, but the best approach is to keep it as low as possible. Although a method to determine glycerin chemically has been described [3], it does not always give consistent results. *Huggins* [4] has championed a 'simulated transfusion' in which the cells are incubated with saline. *Roberts* [5] has proposed the determination of osmolarity but it requires expensive equipment and some time. The simplest, which was suggested to us [6] is to determine the total solids contents of the supernatant with an optical total solids meter.

Although the use of adequate quality control procedures will contribute to a more safe and effective blood unit, there is one extremely important point to remember. The blood components were being given to treat a patient with a specific problem. Certainly, the ultimate quality assurance procedure is an evaluation of the patient's response to the transfusion, and the presence or absence of side effects. Pre- and post-transfusion hemoglobin measurements always should be made; and in those transfusions in which there is an adverse reaction, studies should be carried out to determine its cause, and if it was due to poor preparation of the component. Therefore, a well-functioning reporting system between the blood center and the surrounding hospitals is an absolute requirement and represents the final step in quality assurance of any blood component or derivative.

References

1 Myhre, B. A.: Quality control in blood banking (Wiley, New York 1974).
2 Myhre, B. A.; Nakasako, Y. Y., and Schott, R.: A rapid method for determining the sterility of frozen-reconstituted blood. Transfusion *17:* 195–202 (1975).
3 Greenwalt, T. J. and Steane, E. A.: The measurement of glycerol in the presence of citrate. Transfusion *4:* 206–209 (1964).
4 Huggins, C. E.: Practical preservation of blood by freezing; in Red cell freezing, a technical workshop, p. 45 (AABB, Washington 1973).
5 Roberts, S. C.: Cryopreserved red blood cells. A blood component; in A seminar on blood components (AABB, Washington 1977).

6 Gibson, J.: Personal communication. M.T. (ASCP).

Byron A. Myhre, MD, PhD
Professor of Pathology
University of California
Harbor General Hospital Campus
1000 West Carson Street
Torrance, CA 90509 (USA)

Harold A. Oberman. The singular clinical objective of transfusion of red cells is the augmentation of the patient's capacity for tissue oxygenation. Therefore, the accomplishment of this goal depends upon the number of red cells which survive in the patient following transfusion and their functional integrity.

The number of functionally active red cells which survive after transfusion varies with the volume of blood originally collected, the manner of collection, the hematocrit of the blood donor, the duration and manner of storage of the unit of blood, the serologic compatibility of the unit of the donor red cells with the patient's serum, the manner of transfusion of the unit of blood, and, if red cell components are being administered, the manner of preparation of these components.

The Standards of the American Association of Blood Banks [1] sets forth minimum requirements of safety and efficacy for the red cell-containing products specified in the question. However, I do not believe that it is practical, or necessary, to standardize the indicated products with respect to potency, in a manner analogous to plasma derivatives. As indicated above, there are far too many variables involved, and it would prove cumbersome for each Blood Bank to monitor each unit of blood daily, with corresponding modification of the label, to indicate the number of red cells predictably available for the patient in each unit of blood.

It is self-evident that one may transfuse units of blood which meet acceptable requirements with respect to volume of blood collected, minium donor hematocrit or hemoglobin level and minimally acceptable conditions and duration of storage, yet there may be wide variation in the number of functionally active red cells received by the patient from different units. For example, let us assume that donor A, with a hematocrit of 46%, donates 490 ml of whole blood, while donor B, with a hematocrit of 41%, donates 410 ml of whole blood. Let us also assume that the unit of blood from donor A is transfused during the 5 day of storage, while that of donor B is transfused during the 20th day of storage. The difference in the number of red cells which would survive in the recipient 24 h after transfusion of these units, all other factors being equal, may approach 90 ml!

Such wide variation in the functional capacity of individual units of red cell-containing products is permissible only because of the inexactitude of blood transfusion therapy in the adult patient. In contrast, it is often necessary to be considerably more specific in the management of the neonate. In this situation use of blood less than 5 days old, as well as of devices for exact measurement of volume of blood product transfused, permits somewhat greater control of the number of red cells administered.

Although it is impractical for the blood bank to monitor each unit of blood daily so as to indicate the number of red cells which will predictably survive in the recipient of each unit, the laboratory must ensure more manageable factors which optimize the survival of the transfused red cells. For example, acceptable conditions of storage of the unit of blood must be stringently enforced, and testing for evidence of serological incompatibility, including donor and patient typing, must be precise. In addition, the transfusion should be conducted in such a manner as to assure the survival of the transfused red cells, as by avoiding excessive warming of the unit of blood and preventing contact of the blood with incompatible intravenous solutions.

Not only must there be standardization of those factors which relate to the survival of the red cells, but also there must be minimum standards prepared related to the safety of the product. For example, the risk of transmission of disease through the transfusion must be mitigated, and asepsis must be maintained during both the collection and storage of the unit of blood. Finally, human error must be avoided in all phases of the collection, storage, processing and transfusion procedure.

Although it may seem inconsistent to specify the minimum cellular content of platelet concen-

trates and granulocyte concentrates [1], it should be appreciated that there may be considerable variation in the actual number of such cells in various transfused concentrates. The guidelines for donor selection, blood collection, storage and processing, as well as specification of minimally acceptable post-transfusion survival of red cells, indirectly result in standardization of minimum content of whole blood or red blood cell components.

The above comments relate to all of the products mentioned in the question, since all are transfused to supply red cells to the patient and differ only in terms of removal of plasma, leukocytes or processing solution.

In summary, it is presently impractical to designate the number of functionally active red cells present in each blood container at the time of transfusion. Fortunately, clinical practice has come to accept considerable variation in the number of functioning red cells actually delivered in these red blood cell products; therefore, our efforts have centered on ensuring the safety and viability of the collected red cells.

Reference

1 Standards for Blood Banks and Transfusion Services; 9th ed. (American Association of Blood Banks, Washington 1978).

Harold A. Oberman, MD
Professor of Pathology
Director of Clinical Laboratories and
Blood Bank
University of Michigan
1335 E. Catherine Street
Ann Arbor, MI 48109 (USA)

Scott N. Swisher. The problem of quality control (QC) of red cell products is very different than that which is possible for products such as cryoprecipitate where there is a well-standardized *in vitro* measurement of factor VIII activity. Similarly, QC test for products like serum albumin are based upon a series of *in vitro* characteristics which correlate reasonably well with the expected *in vivo* effect of administration of these products. Even in these cases where *in vitro* QC methods appear to work quite well, they are obviously incomplete. For example, the amount of nonfactor VIII protein is not controlled in cryoprecipitate. The recent problem created by the presence of prekallikrein activator in plasma protein fraction (PPF) preparations reveals the limitation of QC procedures even in the case of well-standardized and well-known products [1].

There are two general approaches to QC of whole blood and red blood cell blood products: (1) control of the process of preparation, and (2) control of the end product itself by testing. All QC procedures for biologics employ some of both approaches. In the case of red cell products, we presently rely primarily on control of preparation. Most of the approved procedures for preparation of red cell products have been validated at some time by the only real reference standard for the final product, *in vivo* red cell recovery and survival after storage. Control of process seems to be satisfactory if all the requirements for preparation, storage and transport of the product have been met. The problem lies in the impracticality of testing the final product for defects which may reflect inadequate adherence to these standards. Periodic scheduled and unscheduled inspections, maintenance of records which reflect important process parameters such as the integrity of storage temperature, and establishment of standards of training for personnel are among the major measures which make process QC effective.

A number of biochemical and biophysical measurements of stored red cells correlate reasonably well with subsequent *in vivo* survival on transfusion. Level of red cell adenosine triphosphate and measurement of deformability by a variety of filtration techniques seem the best of these. However, the correlation does not appear to be close enough to permit utilization of these techniques for QC purposes [3, 4].

Should periodic red cell survival studies be required of virtually every blood bank producing red cell products? The answer is probably no. A relatively large number of such studies would have to be done to detect significant departures from acceptable standards. This is in part due to the inherent variability of red cell survival methods, both biological and technical [2]. It is also doubtful

that human exposures to ^{51}C could be justified for this purpose in the absence of significant evidence of a problem with quality of red cell products.

The same can be said about culturing bloods for contamination with microorganisms. A unit found to be significantly contaminated is such a rare event that a large number of cultures would be required to establish a valid measure of the rate of contamination. Careful inspection of blood units prior to administration seems preferable, with recognition that not all significantly contamined units will be detected by this approach. It might be wise to require culture examination of at least all suspected units with full identification of any isolated organisms as a basis for further epidemiological investigation of the source and mechanism of contamination.

At present, QC of red cell products for hepatitis infectivity is based primarily on the use of 'state of the art' third generation hepatitis B surface antigen tests. There seems to be little added benefit from testing for hepatitis B antibodies. Hepatitis surveillance among recipients with exclusion of implicated donors by use of a registration process and electronic data processing equipment is at present the only technique available for elimination of carriers of non-A, non-B hepatitis from the donor pool, in the absence of a useful serological test for these agents. The need for such a test is self-evident.

Although not strictly a part of product QC, the chain of procedures from patient and donor identification, and determination of ABO and Rh_0 groups, through the cross-match or 'type and screen' procedure to the actual administration of a unit of red blood cells, provides a major opportunity for enhancement of recipient safety. Clerical errors continue to plague the practice of transfusion at this level. Here automation and data processing technology may be the way of the future. The cost of this approach must be justified primarily on the grounds of safety. At present, equipment does not exist which will carry this chain of data to the recipient's bedside. And when it does arrive, it will require a significant experience to be sure this system is truly 'bug free'.

Opinion in the US does not support routine extended blood typing of donor and recipient for additional red cell antigens such as the other principal antigens of the Rh or Kell systems. Granted, some alloimmunizations could be avoided, but these are rarely a serious problem. The cost of extended typing is considerable and the logistic problem is substantially increased for little return in safety.

Of course, all new blood preservation processes or significant changes in established methods should continue to be subjected to evaluation by *in vivo* studies of red cell survival. Improved methods of surveillance of experience with new and old red cell products in the field where they are being used will provide another probably useful approach to QC of these materials.

These and related questions have been considered in depth over the last 3 years by Panel 6 of the Bureau of Biologics, Food and Durg Administration, on Safety and Efficacy of Blood and Blood Derivatives of which the author served as Chairman. The report of this panel will be published in the Federal Register. While not presuming to speak for the Panel officially, the opinions expressed above are in general agreement with positions taken by the Panel [4].

References

1 Alving, B. M.; Hajuna, Y.; Pisano, B. L.; Mason, B. L.; Buckingham, R. E.; Mozen, M. M., and Finlayson, J. S.: Hypotension associated with prekallikrein activator (Hageman-factor fragments) in plasma protein fraction. New Engl. J. Med. *299:* 66 (1978).

2 Mollison, P. L.: Further observations on the normal survival curve of ^{51}Cr-labelled red cells. Clin. Sci. *21:* 21 (1961).

3 Beutler, E.: Experimental blood preservatives for liquid storage; in Greenwalt and Jamieson, The human red cell *in vitro*, p. 189 (Grune & Stratton, New York 1974).

4 Haradin, A. R.; Weed, R. I., and Reed, C. F.: Changes in physical properties of stored erythrocytes. Relationship to survival *in vivo*. Transfusion *9:* 229 (1969).

5 Report of Panel 6, Bureau of Biologics, Food and Drug Administration: Safety and Efficacy of Blood and Blood Derivatives (The Federal Register, in press).

Scott N. Swisher, MD
Professor of Medicine
College of Human Medicine
Michigan State University
East Lansing, Mich. (USA)

Thomas F. Zuck. The question asked is whether or not the same principles applied to the quality control of plasma derivatives should be applied to the quality control of cellular blood components. Developing parameters for cellular products poses three difficulties not encountered in similar endeavors for plasma derivatives. First, cellular components are almost invariably administered as individual units from single donors, whereas plasma derivatives are manufactured from large multidonor pools. Unavoidable interdonor biological variations are leveled by subdividing large plasma pools into individual dosages. This leveling is not possible to achieve with either red cell or cytapheresis products, and only partially possible to achieve through pooling of individual donor units of platelets. Further, the pooling of plasma for derivative manufacture permits a lot assay value to be assigned to multiple individual dosage units, whereas each donor unit of red cells or cytapheresis cell would have to be assayed to achieve the same precision achievable with plasma pools.

Second, cellular components require a suspending medium to facilitate infusion. Some characteristics of these media, such as supernatant potassium concentration, may be as clinically relevant as the cellular parameters. Some, such as hemoglobin concentration, may reflect the tolerance of the cells to storage, but are extremely difficult or impossible to control. Other media characteristics, such as the osmolality of the supernatant of thawed deglycerolized red cells are more practical, and their value more amenable to control.

Table I indicates some measurements which might be contemplated to standardize red cell products, and indicates this writer's opinion of their usefulness and practicality. The assumption has been made that *all* units would have to be assayed shortly prior to infusion, and that all blood banks could perform the assays reliably. The latter assumption is probably overly optimistic. Similar tables could be constructed for all cellular components. Thus, it may not be practical to offer cellular components to the medical profession as 'standardized' in other than the broadest sense of knowing the arithmetic mean values and standard deviations of an adequately studied number of similar products.

Table I. Red cell parameters

Parameter	Useful	Practical[1]
Cellular		
ATP contentration	partially	no
2,3-DPG	unclear	no
In vivo survival	yes	no
p50	unclear	no
Deformability	perhaps	no
Suspending medium		
Residual WBC	selected cases	perhaps
Hemoglobin concentration	selected cases	perhaps
Potassium	selected cases	perhaps
Sodium	selected cases	perhaps
Ammonia	selected cases	perhaps
Osmolality (thawed cells)	yes	no
Screen filteration pressure	perhaps	no
Microaggregate volume	perhaps	yes

[1] Assumes that parameter is to be measured on each individual cell unit and that a sterile entry were possible so the dating period would not change.

Third, whereas *in vitro* assays of properly administered plasma derivatives tend to correlate rather well with *in vivo* performance, the correlation between *in vitro* markers used to product cellular viability and *in vivo* performance is much less precise. This difficulty was illustrated recently by the poor correlation between red cell ATP concentration and the *in vivo* survivability of red cells stored as concentrates in CPD-A1 [1].

It seems that the sheer number of procedures which would be required to 'standardize' individual units of cellular components would make this effort extremely difficult. Any selection of parameters for study should be made with care, with an eye focused on the cost-benefit ratio. Perhaps greater emphasis and resources placed in the area

of postinfusion patient monitoring for the clinical and laboratory effects of cellular components following administration would be of greater benefit in improving hemotherapy practice.

Reference

Zuck, T. F.; Bensinger, T. A.; Peck, C. C.; Chillar, R. K.; Beutler, E.; Button, L. N.; McCurdy, P. R.; Josephson, A. M., and Greenwalt, T. J.: The *in vivo* survival of red blood cells stored in modified CPD with adenine. Report of a multi-institutional cooperative effort. Transfusion *17:* 374–382 (1977).

Thomas F. Zuck, MD
Chief, Department of Pathology
Walter Reed Army Medical Center
Washington, DC 20012 (USA)

Announcement

The Blood Bank Director's Training Program

The New York Blood Center offers a post-doctoral training program for qualified physicians interested in a career in blood transfusion services. It is anticipated that persons completing the program will serve as full-time directors or associate directors of regional blood programs or hospital blood banks, research scientists, medical school faculty members or members of governmental regulatory or advisory agencies.

In the initial year, the training Fellow receives instruction in immunohematology, tissue typing, cryobiology, and protein chemistry in the various laboratories of the Center's Lindsley F. Kimball Research Institute. Experience in regional blood program management is gained through active participation in the Greater New York Blood Program. In addition, each Fellow is assigned to one of several participating, university-affiliated hospital blood banks in New York City for training in clinical blood transfusion therapy and blood bank technology. A second year can be arranged to suit individual requirements for more intensive training in one or more areas.

The program is accredited by the Liaison Committee on Graduate Medical Education of the American Medical Association; the entire year is acceptable towards meeting eligibility requirements for the sub-specialty examination in blood banking of the American Board of Pathology. In addition, it is accredited by the Department of Education of the State of New York (for continuing education) and the Veterans Administration (for reimbursement under the G.I. Bill of Rights). Requirements: (1) An MD degree with a minimum of 2 years' post-doctoral training in clinical medicine or pathology; (2) Qualifications for obtaining a license to practice medicine in New York State by the beginning of the fellowship year; (3) US citizenship or permanent residency. Applications for the program beginning July 1, 1981 must be received before February 1, 1981.

Further information may be obtained from Helen L. Keers, Administrative Assistant, Educational Programs, The New York Blood Center, 310 East 67th Street, New York, NY 10021 (USA).